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A green approach to heterogeneous catalysis using ligand-free, metal-loaded cross-linked cyclodextrins

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Abstract.

In this work we describe the application of a new series of solid cross-linked cyclodextrin (α -, β -, and γ -CD) based catalysts which are obtained by reticulation with hexamethylene diisocyanate (HDI) in solutions containing Pd^(II) or Cu^(I) cations. Diisocyanates are efficient cross-linking agents for CDs owing to their high reactivity towards hydroxyl groups. Metal content in the polyurethane-bridged CD polymers has been analyzed using ICP-MS. Pd^(II) based catalysts have been successfully used in C-C couplings (Heck and Suzuki reactions) and a Cu^(I) based system in alkyne/azide [3+2] cycloadditions. The fact that metal leaching is negligible, which allows it to be recycled, together with its facile preparation make this a truly sustainable protocol. As confirmed by ICP-MS analysis the crude products do not require further purification for metal contamination. This versatile catalyst, due to its polar structure, is particularly suitable for microwave-assisted reactions that, in this study, gave the best yields in shorter reaction times. Due to their polar structure, both native CDs and cross-linked derivatives, are very sensitive to dielectric heating; this effect is enhanced by the embedded cations. The design of sustainable synthetic protocols can be efficiently accomplished using a multi-faceted strategy that combines innovative solid catalysts and suitable enabling technologies.

Key-words: heterogeneous catalysis, Pd^(II)/Cu^(I) catalysts, cross-linked cyclodextrins, Heck and Suzuki reactions, click chemistry.

Introduction

Reticulated CDs have been applied in several fields [1] and a wide range of reactive CD derivatives have been described [2]. In recent years polycyclodextrin derivatives found a number of application as enzyme stabilizers [3], as solid-phase adsorbent of pollutant [4] and for the removal of Cu²⁺ in

aqueous solutions [5]. We studied different reticulation methods with diisocyanates, arylcarbonates and epichlorohydrin [6]. CD reticulation in the presence of metal ions in solution is not unprecedented and recently the preparation of superparamagnetic β -CD-functionalized composite nanoparticles *via* the epichlorohydrin cross-linking of carboxymethyl β -CD-modified magnetite (Fe_3O_4) nanoparticles has been reported [7]. The inclusion phenomenon can occur either in the CD cavity or, otherwise, in other, larger cavities that are generated by the reticulation. The location of the inclusion, of course, depends on the radius of the cations [8] and the type of CD [9]. An alternative solid catalyst preparation method can be found in the simple physical mixture of the metal salt and the polyurethane-bridged CDs in a planetary ball mill. A similar approach has recently been described for chitosan based Pd-catalysts in which the simple physical mixture [10] was compared to metal-loaded cross-linked chitosan [11]. Besides when used in microwave-assisted reactions, this catalyst was strongly activated by ball milling [12], allowing the solid-state Suzuki cross-coupling of poorly reactive (hetero)aryl chlorides with phenylboronic acid to be carried out [13]. Other authors have used several supported metals (Pt, Pd, Rh, and Ru) integrated onto a β -CD polymer (epichlorohydrin) as a catalyst. These were prepared by refluxing a suspension of the corresponding metal salt and β -CD polymer in either a mixed methanol-water or a methanol-NaOH solution [14]. These heterogeneous catalysts were applied in enantioselective olefin hydrogenation. We recently described the preparation and the synthetic application of a new series of metal-loaded (Pd^{II} and Cu^{I}) catalysts which are based on cross-linked native β -CD and reticulated with different diisocyanates under sonication [15]. Excellent yields were observed for Sonogashira reactions carried out in water and glycerol and the catalyst was easily recovered and reused three times without a significant loss in catalytic activity. In the present study we extend the ultrasound-promoted HDI reticulation in the presence of Pd^{II} and/or Cu^{I} salts to α - and γ -CD. These versatile catalysts were tested in several reactions both under conventional heating and MW irradiation. The Pd^{II} loaded polymers were used to perform Heck and Suzuki cross-couplings, while the catalysts that bear Cu^{I} to carry out alkyne/azide [3+2] cycloadditions (CuAAC).

Over the last decade a huge effort has been made in the search for cost-effective, ligand-free Pd or Cu catalysts and new activation techniques to perform highly efficient C-C couplings [16] and click reactions [17]. Simple metal salts, metals supported on active charcoal, or metal-loaded polymers have been efficiently used under ultrasound [18] and microwave (MW) irradiation [10, 11], and even under their simultaneous irradiation [19, 20, 21] which tends to give better results. Although high turnover numbers (TONs) have been attained using heterogeneous catalysts coupled with sophisticated recycling strategies, it would be enormously simpler to use catalysts that are effective at such low levels that, in principle, they may not need to be recovered and recycled. Besides cost

considerations, an important concern is product contamination by the metallic catalyst, which in the case of pharmaceuticals must be strictly controlled (usually not to exceed 10 ppm). Problems of cost and contamination could be solved with catalysts that display TONs of 10^5 or higher [22]. Thus any Pd-based technique with TONs of 10^5 - 10^6 and adequate turnover frequency (TOF) will be of great practical interest for fine chemical and pharmaceutical production [23]. An outstanding contribution to this ambitious task can be found in so called “enabling technologies” that are able to strongly enhance reaction rates even at very low catalyst loads [20]. This is mainly made possible by the optimization of heat and mass transfer and the strict control of all reaction parameters.

Experimental

Chemicals and reactors

Commercially available reagents and solvents were used without further purification unless otherwise noted. All native CDs were kindly provided by Wacher Chemie (Germany). The commercially available sonochemical reactor (high-power cavitating tube working at 21.5 kHz) was developed in collaboration with Danacamerini S.a.s. (Torino, Italy). All critical parameters (power, frequency, reaction temperature and the modified atmosphere) were monitored [24].

Analytics

GC-MS analysis were carried out on a gas chromatograph Agilent 6890 (Agilent Technologies - USA) fitted with a mass detector Agilent Network 5973 using a capillary column with the following characteristics: 30 m long, an i.d of 0.25 mm and a film thickness of 0.25 μ m. The metal content in solution was determined by ICP-MS on a Quadrupole-ICP-MS X Series II (Thermo Fisher Scientific) after the samples had been digested in HNO₃ and aqua regia (1 HNO₃/3 HCl). The oxidation state of the adsorbed palladium or copper was measured using X-ray photoelectron spectroscopy (XPS) with a Quantum 2000 (PHI Co., Chanhassen, MN, USA) with a focused monochromatic Al K source (1486.7 eV) for excitation.

CD catalyst preparation

In a typical poly- α -/ β - or γ -CD/Pd/Cu catalysts preparation, Pd(OAc)₂ (25 mg, 0.22 mmol), or CuCl (25 mg, 0.5 mmol), and α -/ β - or γ -CD (1 g, β -CD = 0.78 mmol) were dissolved in DMF (25 mL) under sonication in a thermostatted sonochemical reactor at room temperature. Hexamethylene diisocyanate (HDI) (1.4 mL, 8.7 mmol) was then added portion-wise and the reaction mixture was kept under sonication at 60°C (21.1 kHz, 60 W) for 30 min. The compact gel was crushed and washed

with water (100 mL), acetone (100 mL), and methanol (100 mL). The product was filtered on a sintered glass Buchner funnel and dried overnight under vacuum at 75°C, to produce a brownish or brownish-green powder (with Pd^(II) or Cu^(I) respectively).

Average metal content in the various cross-linked CDs catalysts was analyzed by ICP-MS, using three different samples from three different preparation batches for each catalyst. The Pd content was 0.53% ±0.02 in α-CD 0.67% ±0.03 in β-CD, and 0.48% ±0.08 for γ-CD, while the Cu content in β-CD was 0.88% ±0.04.

Catalysts application

Heck and Suzuki reactions with 4-bromoacetophenone

a) Styrene (1.5 mmol), 4-bromoacetophenone (1 mmol), K₂CO₃ (1.5 mmol), TBAB (1 mmol) DMA (10 mL) and the polymeric CD catalyst (200 mg) were stirred 3h at 120°C. The mixture was cooled at room temperature under stirring. After filtration and neutralization (dil. HCl), *t*-butylmethylether or dichloromethane (25 mL) was added and the organic layer recovered and evaporated under vacuum yielding the product in high yield (Tables 1 and 2).

b) Phenylboronic acid (1 mmol), 4-bromoacetophenone (1 mmol), Na₂CO₃ (1.5 mmol) (or TEA), water or water:dioxane 9:1 (10-15 mL) and the CD catalyst (50 mg) were stirred 3h at 65°C. The mixture was cooled at room temperature under stirring. After filtration and neutralization (dil. HCl), *t*-butylmethylether or dichloromethane (25 mL) was added and the organic layer recovered and evaporated under vacuum yielding the product in high yield (Table 3).

MW-assisted procedures for Heck and Suzuki reaction under pressure (Tables 1-3)

The same Heck and Suzuki reactions have been carried out in a MW reactor SynthWAVE - Milestone, under N₂ pressure (20 bar) and stirring at 120°C for 1h (power 130 W) and 65°C for 45 min (power 100 W) respectively.

The crude products do not require further purification for metal contamination, in fact ICP-MS analysis showed in all cases a Pd content lower than 6-8 ppm.

Alkyne/azide [3+2] cycloaddition

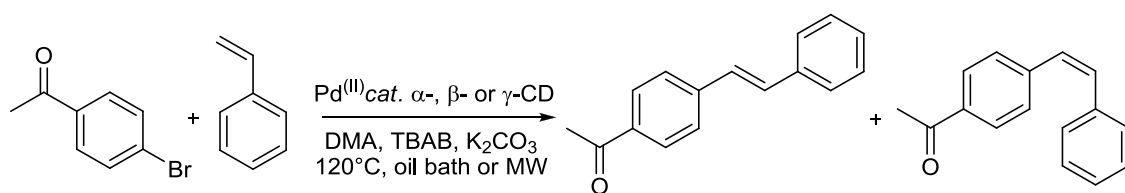
Cu^(I) cross-linked β-CD (150 mg) was added to a solution in H₂O/dioxane 8:2 of benzyl azide (1 mmol) and phenylacetylene (1.5 mmol). The solution was stirred at 70°C for 10 minutes under MW irradiation (100 W), then cooled and filtered off. The filtrate showed complete conversion and the presence of the triazole in high yield (96-98%). The residue catalyst was washed with H₂O and

dioxane, dried over night at 75°C and reused twice with a moderate reduction of activity (about 6-8% less each run) though a Cu content roughly constant (from 0.88% to 0.86-0.87%).

Results and Discussion

Several outstanding authors have shed light on the enormous potential of enabling technologies from the smallest lab scale all the way up to industrial production [25]. Our approach, which combines a catalyst, where the metal is tightly embedded in the cavities of the polymeric CD net, and physical activation with MW irradiation, results in a winning green approach to process intensification.

First we studied the catalytic differences between the three Pd-loaded cross-linked CD catalysts obtained from α -, β - and γ -CD. This study was conducted with the Heck reaction using styrene and 4-bromoacetophenone both under conventional heating and under MW irradiation (Scheme 1).



Scheme 1. General conditions for Heck reaction.

Following the standard procedure described in the experimental part with the same amount of α -, β - and γ -CD/ $\text{Pd}^{\text{(II)}}$ catalyst for each reaction (200 mg), we observed only little conversion and yield differences in the three catalysts (Table 1). This led us to proceed with the β -CD/ $\text{Pd}^{\text{(II)}}$ catalyst, because native β -CD is much cheaper and more easily available. The MW reactor SynthWAVE (Milestone) equipped with a rack with several test tubes (Figure 1), facilitated the search for the optimal catalyst load, solvent ratio and type. MW irradiation brought the reaction to completion in 1 h with all the catalysts. In the search of optimum conditions, the reaction was carried out with a series of aryl halides varying the catalyst amount (Table 2).

Table 1. Heck reaction with styrene and 4-bromoacetophenone: oil bath vs MW heating.

CD-cat	oil bath (3h)	MW (1 h)
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	yield %			yield %		
	conversion	<i>trans</i>	<i>cis</i>	conversion	<i>trans</i>	<i>cis</i>
β	97	94	3	100	96	4
α	92	91	1	99	97	2
γ	96	93	3	100	94	6



Figure 1. The rack with several test tubes in the *SynthWAVE* (Milestone)

The reaction in oil bath was monitored every 30 min, reaching a complete conversion after three hours. Our investigation showed that the optimal amount of β -CD/Pd^(II) catalyst in the Heck reaction was 4 times higher than the Suzuki coupling (200 vs 50 mg).

Table 2. Heck reaction: MW under pressure with different amount of β -CD/ Pd^{II} catalyst

Entry	Aryl-X	β CD-cat (mg)	conversion (%)
1	4-Br-acetophenone	25	30
2	4-Br-acetophenone	50	34
3	4-Br-acetophenone	100	51
4	4-Br-acetophenone	125	54
5	4-Br-acetophenone	150	72
6	4-Br-acetophenone	175	87
7	4-Br-acetophenone	200	100
8	4-Br-anisole	150	89
9	4-Cl-nitrobenzene	150	39
10	4-Cl-acetophenone	150	8
11	4-Cl-acetophenone	300	19

MW irradiation at 120°C for 1 h.

The β -CD/ Pd^{II} catalyst was then tested in Suzuki cross-couplings (Scheme 2) both under conventional heating (3 h) and MW irradiation (45 min); conversion yields are listed in Table 3.

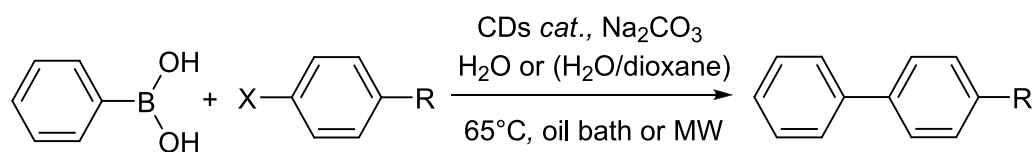
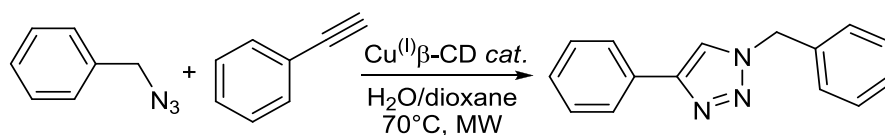
**Scheme 2.** General conditions for Suzuki cross-coupling.

Table 3. Suzuki reaction: oil bath vs MW irradiation under pressure with different amount of β -CD/Pd^(II) catalyst.

Entry	Aryl-X	β CD-cat (mg)	oil bath conv. yield (%)	MW conv. yield (%)
12	4-Br-acetophenone	25	60	64
13	4-Br-acetophenone	30	61	68
14	4-Br-acetophenone	35	70	75
15	4-Br-acetophenone	40	84	86
16	4-Br-acetophenone	45	93	97
17	4-Br-acetophenone	50	99	100
18	4-Br-anisole	45	93	99
19	4-Br-anisole	50	98	100
20	4-Cl-nitrobenzene	45	10	22
21	4-Cl-acetophenone	45	6	15
22	4-Cl-acetophenone	90	25	34

A series of recycling trials using the catalyst recovered from Heck and Suzuki reactions was performed after the catalyst itself was washed and dried under vacuum. Considering that about 10%, in weight, was lost during the entire process, the addition of 20% of new catalyst to the recovered portion gave roughly the same yield as the first run (only 2-3% less) in both reactions. The moderate reduction of activity does not derive however from Pd leaching, in fact ICP-MS analysis showed a roughly constant metal content in the reused samples (0.5-1.5% less).

The β -CD/Cu^(I) catalyst was successfully applied in the most common click reaction, namely the alkyne/azide [3+2] cycloaddition with benzyl azide and phenylacetylene. In previous papers we explored the possibility of entrapping Cu^(I) in other solid supports such as charcoal [26], cross-linked chitosan [11] the possibility of generating this species *in situ* from the sonochemical red/ox between the metallic copper and the copper oxide on the surface was also investigated [27]. The new β -CD/Cu^(I) catalyst, under MW irradiation (70°C, 100 W), brought the reaction to completion in only 10 min.



Scheme 3. General conditions for the click reaction (CuAAC).

Conclusion

We have herein reported a case of ligand-free, metal-loaded polycyclodextrin catalysts, effectually applied in C-C couplings under MW irradiation. The flexible combination of facilitating technologies and suitable supported catalysts enables efficient and sustainable synthetic protocols. This multifaceted strategy may pave the way to the environmentally friendly intensification of several synthetic processes.

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